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10/772,636	02/05/2004	Louise M. Kelly	MPI03-015P1RNOMNIM	5610

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Jean M. Silveri
Millennium Pharmaceuticals, Inc.
40 Landsdowne Street
Cambridge, MA 02139

EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 07/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/772,636	KELLY ET AL.	
	Examiner	Art Unit	
	Zachary C. Howard	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-11,13 and 23-27* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/4/05, 5/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

10-0

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 5/4/05 has been entered in full. Claims 1, 2, 4, 6, 8, 9 and 11 are amended. Claims 12 and 14-22 are canceled. New claims 23-27 are added.

Election/Restrictions

Applicant's election of the following in the reply filed on 5/4/05 is acknowledged:

1) Applicant has elected Group I, claims 1-13, without traverse.

2) Applicant has elected the 965 molecule.

3) Applicant has elected the species of anemia.

With regard to election (2) and (3) above, Applicant did not indicate whether each election was with or without traverse. However, because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, each election (2) and (3) has been treated as an election without traverse (MPEP § 818.03(a)).

New claims 23-27 are deemed to belong to the elected group, Group I.

Claims 1-11, 13 and 23-27, in so far as they are drawn to the 965 molecule and the species of anemia, are under consideration.

Inventorship

In view of the papers filed 5/31/05, the inventorship in this nonprovisional application has been changed by the deletion of: Carroll, Joseph M.; Farlow, Deborah; and Healy, Aileen. The remaining inventor is: Kelly, Louise M.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Specification

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The current title is not descriptive because the claims are directed only to the 965 polypeptide.

The following title is suggested: "Methods using 965 polypeptides for identifying compounds capable of treating hematological disorders"

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13 and 23-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 are indefinite because it is not clear in step (d) what activity the compound must have in order to identify it as "a compound capable of treating a hematological disorder" (claim 1) or "a compound capable of modulating hematopoiesis" (claim 8). Clarity could be added to the claims, for example, by amending step (d) to read, "wherein a compound that causes differentiation of CD34 progenitor cells into mature cells of differentiated hematopoietic cell lineage is thereby identified as a compound capable of treating a hematological disorder."

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Claim 1 encompasses a method for identifying a compound capable of treating anemia and Claim 7 encompasses a method for identifying a compound capable of modulating hematopoiesis. Each method comprises combining a test compound with a sample comprising a genus of polypeptides with sequence similarity to SEQ ID NO: 64, detecting binding of the test compound to the polypeptide, combining the compound with CD34 progenitor cells expressing said polypeptide, and determining if the cells differentiate into mature cells of differentiated cell lineage (claim 1) or proliferate (claim 7). Claims 2-7, 8-11, 13, 23-27 depend from claim 1 or 7 and limit the respective method to particular types of test compound, polypeptide (i.e., fusion protein), sample, cell, hematological disorder, or method of detecting binding.

The prior art teaches that the polypeptide of SEQ ID NO: 64 is a human transmembrane protein-tyrosine phosphatase δ (HPTPδ; see Pulido et al, 1995, cited as reference CE on the IDS submitted 5/4/05). Pulido teaches that HPTPδ mRNA is expressed in human kidney and brain samples, but not in heart, placenta, liver or skeletal muscle samples (see pg 6725). The relevant art does not teach any role for HPTPδ in the differentiation of CD34 progenitor cells.

The instant specification teaches that HPTPδ is expressed at high levels in the brain and expressed at low levels in other tissues and organs (see pg 35). The

specification further teaches, "In hematopoietic cells, 965 mRNA was expressed at the highest levels in CD34 progenitor cells, but not in differentiated hematopoietic cells. In cultures differentiated to myeloid cells, erythroid cells and megakaryocytes, 965 mRNA expression decreases after 24 and 48 hours in culture, indicating that its key role is in CD34 progenitor cells" (same page). The specification further teaches "PTP-δ is selectively decreased in primary hepatomas and hepatoma cell lines, suggesting that it is a tumor suppressor." In view of the expression and function of HPTPδ, the specification concludes, "modulators of 965 would be useful in the treatment of hematological disorders" (same page).

The specification does not provide any examples of compounds for treatment of anemia or any other hematological disorder that were identified by the claimed method. Furthermore, the specification does not teach whether or not HPTPδ actually functions in the proliferation and differentiation of CD34 progenitor cells rather than just being a marker of undifferentiated cells. The process of proliferation and differentiation of hematopoietic stem cells and the molecules involved in this process are poorly characterized. With respect to hematopoietic stem cells, Bonnet et al (2003) teaches "Despite some important progress, the genetic and cellular factors that influence stem cells either to differentiate into developmentally restricted progenitor cells or to self-renew to replace cells that become committed to differentiation, are still poorly understood" (see pg 222 of Bonnet et al, 2003, Birth Defects Research (Part C) 69: 219-229). The relevant art does not teach that an expression pattern wherein a particular gene is expressed in CD34 progenitor cells but has lowered expression in differentiated hematopoietic cells indicates that the gene encodes a protein with a functional role in the differentiation process. Other genes are known that are expressed in a similar pattern, but are not known to have a role in the differentiation process. For example, the CD34 molecule is expressed on the CD34 progenitor cells and is down-regulated in hematopoietic cells. Bonnet teaches, "the normal function of the CD34 molecule in hematopoiesis has remained enigmatic" and "both mouse and human CD34 are expressed outside the hematopoietic system" and "this distribution suggest a function outside hematopoiesis" (see pg 221). As taught by the prior art and the instant

specification, the HPTPδ molecule is highly expressed in the brain. Therefore, in view of the teachings of Bonner, one of skill in the art would conclude that it has a function outside of hematopoiesis. While this would not necessarily rule out a role in hematopoiesis, it would lead one of ordinary skill in the art to conclude it was unpredictable whether or not HPTPδ actually has a role in hematopoiesis. Therefore, in order to use the method as claimed to identify compounds with a role in treatment of a hematological disorder, one of ordinary skill in the art would need to first determine whether or not HPTPδ actually plays a role in hematopoiesis, such that a modulator of HPTPδ would cause proliferation and differentiation of CD34 progenitor cells.

It is acknowledged that the level of skill of those in the art is high, but it is not disclosed and not predictable from the limited teachings of the prior art and specification whether or not the HPTPδ polypeptide of the present invention could be used to screen for compounds for treatment of any hematological disorder such as anemia. There are no examples of compounds for treatment of anemia identified by said method. Thus the specification fails to teach the skilled artisan how to use the method to identify compounds for treatment of anemia without resorting to undue experimentation. The specification has not provided the person of ordinary skill in the art the guidance necessary to be able to use the method for the above stated purpose.

Due to the large quantity of experimentation necessary to determine if the method could be used to screen for molecules for modulating hematopoiesis, the lack of direction/guidance presented in the specification regarding same, lack of working examples and the teachings of the prior art and the complex nature of the invention, undue experimentation would be required of the skilled artisan to use the claimed invention. What Applicant has provided is a mere wish or plan and an invitation to experiment.

Even if the claimed method was enabled for use with a polypeptide of SEQ ID NO: 64, the claims would still be rejected under 35 U.S.C. 112, first paragraph because 1) the claimed methods encompass use of polypeptides other than SEQ ID NO: 64; and 2) the claimed methods encompass use of transgenic animals.

1) Each of the claimed methods encompass polypeptide variants of SEQ ID NO: 64. The genus of variants includes polypeptides that are 95% identical to SEQ ID NO: 64 and polypeptides encoded by polynucleotides at least 95% identical to SEQ ID NO: 63. A polynucleotide of SEQ ID NO: 63 has 6263 nucleotides. Therefore, the genus of polynucleotides that are 95% identical to SEQ ID NO: 63 includes those with 5950 identical nucleotides, or in other words, those polynucleotides with up to 313 changes to the polynucleotide of SEQ ID NO: 63. The open coding region of SEQ ID NO: 63 is 5736 nucleotides, or 1912 codons, in length. Therefore, the genus of polynucleotides that are 95% identical to SEQ ID NO: 63 includes those with a change in 313 different codons of SEQ ID NO: 63. As the encoded protein is 1912 amino acids in length, this represents a protein with 313 changes to the amino acid sequence, or 16.4% of the sequence of SEQ ID NO: 64. Therefore, the genus of polynucleotides that are 95% identical to SEQ ID NO: 63 includes polynucleotides encoding proteins that are at least 83.6% identical to SEQ ID NO: 64.

The claims encompass variants of a protein of SEQ ID NO: 64 in which one or more amino acids are substituted, deleted, and/or inserted. None of the claims include the limitation that the polypeptide variants exhibit characteristics of the parent polypeptide of SEQ ID NO: 64. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible variants of polypeptides of SEQ ID NO: 64. The specification has not provided a working example of the use of a variant of the polypeptide of SEQ ID NO: 64, nor sufficient guidance so as to enable one of skill in the art to make such a variant. The specification has failed to teach which amino acids of SEQ ID NO: 64 could be modified so as to produce a polypeptide that is not identical to SEQ ID NO: 64 and yet still retain the activity of the polypeptide of SEQ ID NO: 64 - which has apparently not been disclosed.

Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the protein corresponding to SEQ ID NO: 64 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 64 is to have a structure and function similar to the protein corresponding to SEQ ID

NO: 64, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 64. Conversely, if a protein variant of SEQ ID NO: 64 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-

dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

2) The claims are directed to methods using a broad genus of cells expressing a polypeptide of SEQ ID NO: 64. The specification contemplates a) assays using isolated host cells and b) assays using animal-based models. These assays are described on pages 64-76 of the specification.

a) The specification contemplates methods using isolated host cells in culture expressing the polypeptide recombinantly (see pg 72-74). The specification and prior art provide specific guidance on how to make host cells expressing SEQ ID NO: 64.

b) The specification also envisions method using transgenic animals expressing a polypeptide of SEQ ID NO: 64 (see pg 64-72). The specification teaches that any

technique known in the art may be used to introduce a transgene into animals to produce the founder lines of transgenic animals (pg 66, lines 10-13). However, there are no methods or working examples disclosed in the instant application whereby a multicellular animal with the incorporated claimed gene (SEQ ID NO: 63) is demonstrated to express the encoded peptide. There are also no methods or working examples in the specification indicating that a multicellular animal has the claimed gene "knocked out". The unpredictability of the art is *very high* with regards to making transgenic animals. For example, Wang et al. (Nuc. Acids Res. 27: 4609-4618, 1999; pg 4617) surveyed gene expression in transgenic animals and found in each experimental animal with a single "knock-in" gene, multiple changes in genes and protein products, often many of which were unrelated to the original gene. Likewise, Kaufman et al (Blood 94: 3178-3184, 1999) found transgene expression levels in their transfected animals varied from "full" (9 %) to "intermediate" to "none" due to factors such as "vector poisoning" and spontaneous structural rearrangements (pg 3180, col 1, 2nd full paragraph; pg 3182-3183). Additionally, for example, the specification discloses that a possible technique used to introduce the claimed transgene into animals is microinjection or retroviral infection. However, the literature teaches that the production of transgenic animals by pronuclear microinjection of embryos suffers from a number of limitations, such as the extremely low frequency of integration events and the random integration of the transgene into the genome which may disrupt or interfere with critical endogenous gene expression (Wigley et al. Reprod Fert Dev 6: 585-588, 1994). The inclusion of sequences that allow for homologous recombination between the transgenic vector and the host cell's genome does not overcome these problems, as homologous recombination events are even more rare than random events. Other methods for developing transgenic animals have been developed but have serious limitations (see pg 21 of Machaty et al 2002, Cloning and Stem Cells, 4(1): 21-27). Therefore, in view of the extremely low frequency of both targeted and non-targeted homologous recombination events in microinjected embryos, and the limitations of other methods of transgenic animal production, it would have required undue experimentation for the

skilled artisan to have made any and all transgenic non-human animals according to the instant invention.

The examiner has interpreted the claims as reciting the step of administering the compound to a subject for detection of binding and/or CD34 progenitor cell proliferation/differentiation. The specification does provide any guidance or working examples of administration of any compound. Due to the unpredictable effects of the compound *in vivo*, it would require a large quantity of experimentation to determine the quantity of compound to be administered, the most effective administration route, and the duration of the treatment.

Due to the large quantity of experimentation necessary to generate a transgenic animal expressing SEQ ID NO: 64 and to introduce and express the claimed nucleic acid in a cell of an organism and to determine appropriate dosage, duration, and type of administration for the compound, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated sample comprising a polypeptide..." and "An isolated CD34 cell..." because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture as described in context a) above.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1-11, 13 and 23-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. § 112, paragraph 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.
Claims 1-11, 13 and 23-27 are genus claims because the claims are directed to methods using variant polypeptides and polynucleotides encoding variant polypeptides. Each genus is highly variant because a significant number of structural differences between genus members are permitted. For example, the claims encompass polypeptides that are 95% identical to SEQ ID NO: 64. The claims also encompass polypeptides encoded by polynucleotides at least 95% identical to SEQ ID NO: 63, which translates to proteins that are up to 83.6% identical to SEQ ID NO: 64 (as explained above in the rejection under 35 U.S.C. § 112, 1st paragraph, enablement). Therefore, the claims encompass variants of a protein of SEQ ID NO: 64 in which one or more amino acids are substituted, deleted, and/or inserted. The claims do not require that the polypeptides possess any particular conserved structure or function, or other disclosed distinguishing feature. The claims only require the claimed polypeptides to share some structural similarity to the isolated nucleic acid molecule of SEQ ID NO: 64. Thus, the claims are drawn to a genus of methods using polypeptides defined only by sequence similarity to SEQ ID NO: 64. However, the instant specification fails to describe the entire genus of polypeptides used in the methods that are encompassed by each of these claims.

From the specification, it is clear that Applicants has possession of a polypeptide of SEQ ID NO: 64. The specification fails to describe or teach any other polypeptide which lacks the sequence of SEQ ID NO: 64 and retains the function of SEQ ID NO: 64. The claims, however, are not limited to a method with the specific polypeptide of SEQ ID NO: 64.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides to be used in the claimed methods. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the

'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only polypeptide of SEQ ID NO: 64, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

With respect to claims 5 and 27, the claims also fail to comply with the written description requirement for a genus of hematological cells comprising the polypeptide of the invention. The specification teaches, in paragraph 16 that "a hematological cell can include, but is not limited to a bone marrow cell, a hematopoietic stem cell, an erythroid cell including a red blood cell, lymphoid cells including B- and T-cell, a myeloid (neutrophil) cell including a monocyte, a granulocyte, and a megakaryocyte. Therefore, the genus encompasses any blood cell expressing a polypeptide of SEQ ID NO: 64. The specification on page 35 teaches that the mRNA encoding SEQ ID NO: 64 is expressed in CD34 progenitor cells, but not in differentiated hematopoietic cells. The specification fails to describe or teach any hematological cell other than CD34 progenitor cells that express a polypeptide of SEQ ID NO: 64. Therefore, while it is clear that Applicants has possession of a CD34 progenitor cell expressing a polypeptide of

SEQ ID NO: 64, Applicant is not in possession of the genus of hematological cells expressing SEQ ID NO: 64. Therefore, only CD34 progenitor cells, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112, 1st paragraph, new matter

Claims 1-11, 13 and 23-27 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement because the claims contain new matter.

Claim 1 was amended 5/4/2005 such that the claim encompasses a method for identifying a compound capable of treating a hematological disorder comprising four steps (a-d). Prior to amendment, the claim comprised two steps: (a) combining a test compound with a polypeptide and (b) detecting binding of the test compound to the polypeptide. In the amended claim, part (a) is amended to include a polypeptide found in a sample and the following new steps are added: (c) combining the compound selected in part (b) with CD34 progenitor cells expressing the polypeptide and (d) determining if the cells differentiate into mature cells of differentiated hematopoietic cell lineage.

The comments by Applicants indicate that support for the amended claims can be found at page 35, lines 9-25; page 46, lines 28-33; page 47, line 21 through page 48, line 2; at page 50, line 30 through page 52, line 8; page 124, line 18; and at page 137, line 20. However, the reference pages do not provide support for the amended claims. Page 35 lines 9-25 teaches the expression pattern of the polypeptide of SEQ ID NO: 64 in tissues, and asserts that inhibition of PTP-δ function (unspecified) would lead to increased proliferation of CD34 progenitor cells, that PTP-δ would be useful in screening for modulators of 965 activity, and that said modulators being useful in treating hematopoietic disorders. Page 46, lines 28-33, teaches in very broad terms that

the 965 polypeptide (SEQ ID NO: 64) can be used to screen for compounds which bind to or modulate activity of the polypeptide. Page 47, line 21 through page 48, line 2, teaches that test compounds can be screened for the ability to modulate 965 activity. Page 50, line 30 through page 52, line 8, teaches 1) that the assay can be a cell-based assay wherein the cell is contacted with a test compound and the ability to modulate the activity of 965 is determined, 2) that determining the ability to modulate can be accomplished by determining the ability to bind or interact with 965, and 3) that determining the ability to bind or interact can be accomplished by one of described methods for determining direct binding. Page 124, line 18, teaches that the genus of isolated nucleic acid molecule used in the method of the invention includes those with 95% identify to SEQ ID NO: 63. Page 137, line 20, teaches that the genus of proteins used in the method includes those with 95% identity to SEQ ID NO: 64.

None of the referenced sections of the specification provide support for amended claim 1. Specifically, the referenced sections do not teach a multi-step method wherein a molecule that is first determined to bind 965 is then screened for the ability to cause differentiation of CD34 progenitor cells into differentiated hematopoietic cell lineage. Furthermore, the Examiner cannot find any support for this method in any other section of the specification. There is no conception of the specific method in the specification, nor does the concept of the specific method flow naturally from the disclosure of the specification. Therefore, the specification as originally filed lacks support for the method encompassed by amended claims 1 and 8. Claims 2-7, 9-11, 13, and 23-27 each depend from claim 1 or 8 and therefore include the limitations of the parent claims.

Claims 24 and 26 were newly added 5/4/2005, depend from claim 1 or 8, and add the limitation that activity is assayed by phosphatase assay (in order to determining binding of the test compound to the polypeptide). None of the referenced sections of the specification provide support for a phosphatase assay. Specifically, the referenced sections do not teach determining the activity of a protein by phosphatase assay. Furthermore, the Examiner cannot find any support for this method in any other section of the specification. There is no conception of a phosphatase assay in the specification, nor does the concept of the specific method flow naturally from the disclosure of the

specification. Therefore, the specification as originally filed lacks support for the method encompassed by newly presented claims 24 and 26.

Art of Note

The polypeptide used in the claimed method, SEQ ID NO: 64, is well-known in the prior art as human transmembrane protein-tyrosine phosphatase (HPTPδ; see Pulido et al, 1995, cited as reference CE on the IDS submitted 5/4/05). The Examiner could find no prior art teaching, or rendering obvious, the use of said polypeptide in a method for identifying a compound for treating a hematological disorder or for modulating hematopoiesis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 571-272-0829. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER